Monograph Report

No 3

Risk Assessment of Occupational Chemical Carcinogens

January 1982

ISSN-0773-6347-3

ECETOC

MONOGRAPH N° 3

BRUSSELS, JANUARY 1982

MONOGRAPH No.3

RISK ASSESSMENT OF OCCUPATIONAL CHEMICAL CARCINOGENS

European Chemical Industry
Ecology & Toxicology Centre

ISSN - 0773 - 6347 - 3

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FOREWORD

The ECETOC Monograph «A Contribution to the Strategy for the Identification and Control of Occupational Carcinogens», was published in September 1980. This set out specific recommendations for the control of occupational carcinogens using the general principles which are applied to the identification and control of any toxic hazards. The monograph was well received as a useful contribution to defining the issues and principles which are key contributors to the strategy of identifying and controlling chemical carcinogens, and to date over 2,200 copies have been issued.

In the current Monograph «Risk Assessment of Occupational Chemical Carcinogens», is reported the work of two further Task Forces completing the study of Hazard Identification and proposing an approach to the very difficult subject of Risk Assessment which it is hoped will be helpful to all those in industry, trade unions, government, international organisations and universities who are responsible for, or are concerned about, the protection of people from occupational carcinogens. As the studies developed it became apparent that the terminology used in the previous Monograph to describe the three-stage approach should be modified, and in this Monograph the subject is reported under the headings Hazard Identification, Risk Estimation and Risk Limitation.

ECETOC has published a number of papers on current toxicological and ecotoxicological issues, a list of which is given in Appendix 4. Copies are available on application to the Executive Secretary.

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SUMMARY

In a previous Monograph («Contribution to the Strategy for the Identification and Control of Occupational Carcinogens», September 1980) a three-stage process for identifying and controlling occupational chemical carcinogens was proposed, and a classification of chemical carcinogens was described as part of the first (essentially qualitative) stage, Hazard Identification, which is completed in this Monograph by an account of the sequence of steps necessary to establish the presence or absence of carcinogenic potential. Then follow details of the second stage, Risk Estimation, in which are taken into account the mode of action of carcinogens, the carcinogenic potency and the factors relating to human exposure. The carcinogen is categorised as being of high, medium or low potency, and by relating this to the exposure conditions the risk is characterised in as quantitative a manner as possible.

Hazard Identification and Risk Estimation should be carried out by a group comprising toxicologists and other experts from all necessary disciplines.

In the final (Risk Limitation) stage the information from Risk Estimation is considered, together with technological, social and economic factors, by a wider group of the parties ultimately concerned with implementing the recommendations made to control the risk, plus experts from the Risk Estimation stage. This group recommends exposure levels or working conditions such that the carcinogenic risk is controlled by means which are technologically feasible and take into account the social and economic consequences of the measures proposed.

A. INTRODUCTION AND DEFINITIONS

A few terms which it is essential to clarify at the outset of any discussion of risk assessment and carcinogenicity are defined below :

Toxicity is the inherent property of a chemical to cause an adverse biological effect.

Cancer is a malignant neoplasm with autonomous growth and certain pathological characteristics which include atypia, invasive growth and, frequently, metastasis.

Carcinogenic potential is the inherent property of a chemical which enables it to produce a cancer under appropriate conditions.

Carcinogenic potency is the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration.

Carcinogenic hazard is the existence of a situation with a potential for causing cancer.

Carcinogenic risk is the probability that a certain population under specified conditions of exposure will develop an increased incidence of cancer. (This risk can only be estimated ; hence the term Risk **Estimation** used in this Monograph).

In the ECETOC Monograph No. 2, three stages in the overall process of risk assessment for occupational chemical carcinogens were noted. As work on the present Monograph progressed it became clear that the three stages were more appropriately entitled :

Hazard Identification

Risk Estimation

Risk Limitation

in line with current usage of the terms «hazard» and «risk». Such nomenclature is adopted in this Monograph, in which the scientific and technical bases for Hazard Identification and Risk Estimation are presented in some depth. Risk Limitation, of which the above scientific and technical input is only a part, is not examined in any detail.

Hazard Identification. The aim of this first stage in risk assessment is to establish qualitatively whether a carcinogenic hazard exists. A chemical is classified, according to the evidence concerning its carcinogenic potential, as a Proven, Putative or Questionable Human Carcinogen.

To achieve this classification, information on carcinogenic potential needs to be developed in a sequence of steps as described in section B. 2.

Such a classification is essential for identifying Proven and Putative carcinogens for which risk assessment is necessary. Classification as Questionable in the early stages of Hazard Identification indicates that more work is required to permit a re-classification into one of the other classes, or a decision that for practical purposes the chemical should be considered as a non-carcinogen for humans — see section B. 1.

Risk Estimation. Once a carcinogenic hazard (i.e. situation with a potential for causing cancer) has been identified it is necessary to quantify as far as is possible the carcinogenic potency of the substance and the factors relevant to human exposure at the workplace. By relating these, the risk is characterised in as quantitative a way as possible. Both the collection of the necessary information and the characterisation of the risk are considered to constitute the Risk Estimation stage.

Risk Estimation is feasible only for Proven and Putative Human Chemical Carcinogens because by definition there is insufficient evidence for chemicals in the Questionable class. In making a Risk Estimation there is a practical requirement to distinguish between carcinogens of widely-differing potency in spite of the many limitations in the expression of such potency. This can be achieved by a group of experienced scientists capable of assessing the various factors involved. By relating the potency of a carcinogen to that of other Human or Putative carcinogens it can be categorised as of high, medium or low potency. This process is described in section C. 1. Factors necessary for assessing human exposure to the chemical at the workplace, also necessary in Risk Estimation, are detailed in section C. 2. It is emphasised that very rarely is sufficient evidence available to enable a Risk Estimation to be expressed numerically in such terms as «a 1 in 10^6 risk of cancer at an exposure of 10 ppm». The question therefore becomes more one of expert judgement than of mathematics. This is why the term Risk **Estimation** is used.

Hazard Identification and Risk Estimation are tasks for an experienced group of toxicologists, and other experts from all necessary disciplines.

Risk Limitation : the information from the Risk Estimation stage is considered, together with important additional factors such as the social and economic consequences, technological feasibility, etc, and a final recommendation for an exposure level and/or working conditions is made.

This is a task for a group comprising representatives of the parties ultimately concerned in implementing the recommendations made to control the risk, plus experts from the Risk Estimation group.

Although this Monograph deals with chemical carcinogens at the workplace, much of the material is generally applicable to the assessment of public risk from chemical carcinogens, the sections dealing with classification, sequence of steps for the identification of carcinogenic potential, and estimation of potency being particularly relevant.

B. HAZARD IDENTIFICATION

To identify the carcinogenic risk which might arise from exposure to a chemical, the carcinogenic potential of that chemical must first be carefully assessed. Carcinogenic potential (not to be confused with potency) is the inherent property of a chemical which enables it to produce a cancer under appropriate conditions. It is revealed only by appropriate observations of the carcinogenic effect on humans or in suitable experimental systems. Accumulated data may allow the chemical to be classified into one of a number of classes. A classification system, and the sequence by which data on carcinogenic potential are developed, are described in the following sections.

B. 1. CLASSIFICATION OF CARCINOGENS

Carcinogens can, according to the extent and quality of the evidence available, be classified as follows.

Proven Human Chemical Carcinogen : «A proven human chemical carcinogen is a substance for which a causal relationship has been established between previous exposure and the occurrence of malignant neoplasms in man».

Putative Human Chemical Carcinogen : «A putative human chemical carcinogen is a clearly-defined chemical substance which causes malignant neoplasms in adequate animal experimentation, under exposure conditions which correspond to those in man or where the relevance of the exposure conditions can be deduced».

Questionable Human Chemical Carcinogen : «A questionable human chemical carcinogen is a clearly-defined chemical substance for which there is incomplete evidence of carcinogenicity, which is based on either (a) observations in man which are suggestive, but do not allow a firm conclusion of a causal relationship between previous exposure and the occurrence of malignant neoplasms ; or (b) findings obtained in animal experiments in which the experimental model is not appropriate to conditions in man and therefore the result cannot be regarded as relevant ; or (c) positive findings in at least two standardised short-term tests, with unrelated end-points, which have been verified as useful for screening for carcinogenic potential».

Such a classification is important since risk assessment is possible only with chemicals in the Proven and Putative classes. The same **principles** should be adopted for both Proven Human and Putative Human carcinogens, but such a classification emphasises that any well-established, relevant differences between man and test animals must be taken into account during this assessment of chemicals in the Putative class and such chemicals cannot automatically be regarded as being in the Proven Human class. Classification of chemicals in the Questionable class means that, by definition, carcinogenic risk assessment is not possible. For such chemicals more evidence should be collected so that they can be reclassified into the Human or Putative class, or considered as a Human Chemical Non-carcinogen (see Monograph No. 2 : «An ultimate proof of non-carcinogenicity is impossible. However, a clearly-defined chemical substance which has consistently shown negative results in adequate studies in man, or adequate animal experimentation, should be considered as a Human Chemical Non-carcinogen for practical purposes»).

This classification of carcinogens should be carried out by a group of experienced scientists. Because of the number and variety of factors which have to be taken into account, no rigid procedure for the classification can be laid down and each chemical has to be dealt with individually.

B. 2. SEQUENCE OF STEPS FOR ESTABLISHING THE PRESENCE OR ABSENCE OF CARCINOGENIC POTENTIAL OF A CHEMICAL

This section is intended to give guidance to those who need to establish evidence as to whether a substance is a chemical carcinogen.

B. 2. 1. Introduction

A wide range of techniques contributes to the assessment of carcinogenicity. The complexities of the toxicological factors, and others such as limited availability of expertise, resources, time, etc, and their interrelationships, make necessary a sequential approach with progressive accumulation of data on which judgements of carcinogenic potential can be made.

The precise sequence of steps in evaluating the presence or absence of carcinogenic potential may vary from chemical to chemical, and many inter-related considerations influence the choice of steps. The conditions of human exposure, the existence of other priorities, and legal or economic considerations may interfere with purely toxicological decisions to move from one step to the next. Nevertheless, this case by case approach is also justified for toxicological reasons, amongst which are :

a) the large differences in carcinogenic properties and potency of chemicals,

b the variety of mechanisms of cancer induction,

c) the diversity of tumour responses in different species and tissues,

d) the differences, from one chemical to another, in the relevance of the experimental models used for extrapolation to man.

Thus to implement any rigid, standardised or obligatory sequence of steps may lead in some cases to the performance of inappropriate studies, while in other cases key studies would not be undertaken. Therefore, to preserve indispensable flexibility this document provides general principles rather than specific recommendations, as guidance for choosing the sequence of steps most appropriate for a particular chemical.

B. 2. 2. Guidelines

The evaluation of the presence or absence of carcinogenic potential is not an isolated process, but is part of an overall evaluation of the toxic properties of a chemical. As the knowledge of these properties accumulates, more or less well-defined phases of advancement in our understanding of the carcinogenicity (or non-carcinogenicity) of a substance can be identified. These phases are logically, but not necessarily sequentially, related and in general provide increasing degrees of confidence in decisions taken about carcinogenic potential.

For each phase a survey is given of : the studies required, the reliability of the results so obtained for the assessment of carcinogenic potential (given in **bold**) ; and the role of these data in preparing for the next phase.

B. 2. 2. 1. Pre-experimental phase.

Before experimental studies are started it is essential to carry out a comprehensive evaluation of the literature. In the absence of published evidence of carcinogenic potential, the substance under consideration should first be examined for structural features which might relate it to compounds with or without carcinogenic potential.

It should be emphasised that with our present knowledge, the use of structure-activity relationships to predict carcinogenic potential is of limited reliability. Therefore, at this phase any assessment of carcinogenic potential can have only a limited value.

Structural considerations may help in choosing suitable experimental designs, e.g. it is important that the chemical class or structural group to which a substance belongs should be taken into account in deciding which short-term carcinogenicity screening tests should be used.

B. 2. 2. 2. Phase of carcinogenicity and toxicity screening.

In this phase, information will be acquired about the activity of a chemical in short-term tests for predicting the presence or absence of carcinogenic potential (see Appendix 1), and about relevant aspects of its toxicological profile.

Many short-term techniques with different methodologies and different end-points have been developed ; others are still under development. They involve the investigation of effects on genetic material (e.g. gene mutation, chromosome aberration, unscheduled DNA synthesis, sister-chromatid exchange), cell transformation, and the induction of preneoplastic or neoplastic lesions. Criteria for selecting valid short-term tests and for drawing conclusions from the results were published in the earlier Monograph and are given here in Appendix 1.

It should be recognised that the majority of the methods available have not been properly assessed for their predictive value in detecting carcinogenic potential. Therefore, the attempts which have been made to arrange these methods into hierarchical tier-systems should not be relied upon.

At this phase other aspects of the toxicological profile may be useful, e.g. data on bioavailability, metabolism, cellular or functional targets (e.g. hormone balance and immunological status) and species differences. Such assessments of toxicity should preferably be made after repeated administration and with a knowledge of dose-effect relationships. These data, together with the results of short-term tests for carcinogenicity, are used in the assessment of carcinogenic potential, and in the development of views on the need for investigations in the next phase.

This screening phase may allow the chemical under consideration to be classified as a «questionable human chemical carcinogen». The quality of the assessment of carcinogenic potential possible at this phase depends on the consistency of all the available results.

While consistently negative results in the carcinogenicity screening phase do not constitute proof of non-carcinogenicity, further studies may not be required unless exposure criteria (intensity, frequency and duration of exposure ; extent of absorption ; other properties of the chemical ; its importance, etc) indicate the need for greater reliability in assessing the presence or absence of carcinogenic potential.

When consistently positive indications of carcinogenic potential are obtained in this phase, consideration should be given to carrying out long-term animal studies.

If an unconfirmed result is obtained, expert judgement is required to decide on an appropriate course of action (see Appendix 1). Under normal circumstances, data on the next phase are required to allow a more accurate assessment to be made.

Factors other than carcinogenic and toxicological properties may rule out the need to go to the next phase of testing. For example, a variety of reasons may lead to complete withdrawal of a chemical from the market or to stopping the development of a new chemical. On the other hand, a decision not to go to the next phase of testing may be taken if the probable human exposure to the chemical is insignificant in relation to its assumed carcinogenic potential.

The design of adequate long-term animal experiments should be based upon essential data that are being collected during this phase. These include : exposure conditions, choice of the appropriate route of administration, selection of species and the choice of the highest dose level.

B. 2. 2. 3. Phase of long-term animal experimentation.

Short of adequate epidemiological data, this phase represents the ultimate stage of establishing the presence or absence of carcinogenic potential of a chemical. Model systems should be used which either mimic closely the human situation, or have demonstrable relevance to it. The animals, of the same strain as those used in the long-term carcinogenicity study, should be monitored for long-term general toxic effects. This monitoring, covering the range of dose levels used in the carcinogenicity study, can be indispensable in interpreting the observed response in target organs.

The different requirements of carcinogenic and chronic toxicity studies can lead to very different protocol designs. This is especially true in setting the highest dose level, and the number of animals to be used.

At the end of this phase an assessment of the carcinogenic potential of a chemical substance can be made on the basis of all available data.

B. 2. 2. 4. Phase of evaluation of observations in man.

The collection and evaluation of observations on people exposed to chemicals is the only method which provides unequivocal evidence of the carcinogenicity of chemicals to man. While the finding of such evidence on a particular chemical carcinogen means that the opportunity of preventing cancer has been lost for some of the population at risk, the identification of a «proven human chemical carcinogen» provides the opportunity to prevent the occurrence of future cases once suitable control measures are taken. Observations in man are also valuable for confirming the lack of carcinogenic activity, and for evaluating the effectiveness of the preventive measures taken against a chemical carcinogen.

Human data related to chemical carcinogenesis range from the incidental recognition and accumulation of individual cases in an exposed population to formal epidemiological studies. The accumulation of individual cases may sometimes constitute convincing evidence, e.g. for those chemical carcinogens inducing otherwise rare types of cancer or cancers with an unusually short latency time.

The formal epidemiological studies comprise case-control studies (or retrospective studies) and cohort studies. Cohort studies may be historical or prospective. In the former, the vital status of people exposed in a sufficiently remote past is established and cancer incidence is compared with that of unexposed groups. The latter studies start with an unaffected group which is followed-up during a sufficiently-long period of exposure. It is obvious that prospective cohort studies are not suitable for identifying the carcinogenic potential of «new» chemicals. If cancer is detected, exposure has already taken place for quite some time because for most chemically-induced cancers in man the latency period is a significant proportion of the life-span. However, prospective studies are well suited to check the adequacy of protective measures taken against a known carcinogenic risk.

The different types of epidemiological studies are not equally reliable. Whenever possible, cohort studies with age-, sex- and time-adjusted standard mortality ratios are preferred. The value of these studies is highly dependent on the accuracy of the exposure and health data, as well as on the suitability of the control group. However, they seldom demonstrate unambiguously a cause-effect relationship between exposure and the induction of neoplasms. By the laws of probability a small but statistically-significant excess of at least one type of cancer may randomly occur when comparing the mortality pattern of two groups. In most cases excess cancer incidence can confidently be attributed to a selected chemical if this excess is consistent, specific and clearly relates to particular exposure conditions. Any conclusion about a possible cause-effect relationship is often confounded by the fact that human groups are usually exposed to more than one chemical. In most cases only correlations which provide a lead for further examination can be established. Additional toxicological data may be needed to identify individual substances responsible for an observed carcinogenic effect in people exposed under complex physical and chemical environmental conditions.

If a clear-cut cause-effect relationship can be established at the end of this phase, the chemical can be classified as a «Proven human chemical carcinogen» and the data can be used directly for Risk Estimation.

C. RISK ESTIMATION

C. 1. EVALUATION OF CARCINOGENIC POTENCY

C. 1. 1. Introduction

Carcinogenic potency is the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration. In the process of estimating the carcinogenic risk of chemicals to man, the determination of carcinogenic potency to man and the conditions of exposure in particular circumstances are the most important elements. It is stressed that carcinogenic potency can be assessed only for chemicals classified as Proven or Putative Human Carcinogens (see definitions in section B. 1).

Human data suitable for potency estimation can be obtained only when reliable exposure data and the health status of the exposed individuals are known with the necessary precision over a sufficient period of time. For the majority of chemicals the carcinogenic activity can be assessed only in animal experiments in which malignant tumours are induced under circumstances of exposure that are relevant to the human situation, or where this relevance can be deduced. There are limitations in using such experiments for potency estimations, the main one being the difficulty of extrapolation from experimental species to man. Carcinogenic activity may be markedly influenced by species-specific characteristics, some of which, such as metabolism and kinetics, will be discussed in more detail below.

In spite of these limitations in the expression of potency there is a practical requirement to make a distinction between carcinogens of widely-differing potency. This can be achieved by considering the various factors discussed here and expressing the potency of a carcinogen as high, medium or low in relation to that of other Proven or Putative Human Carcinogens.

C. 1. 2. Terms for Expressing Potency

The terms used to express the potency of any toxic activity are a function of dose and intensity of effect. In the case of carcinogens the expression of both dose and intensity, or incidence, is so complex as to preclude the calculation of a simple numerical index. The ideal expression of dose would be the concentration, integrated over time, of the ultimate carcinogen at the critical target site. This expression of dose is dependent on the frequency, magnitude, duration and route of exposure and the interaction of these factors with metabolic processes and kinetics which affect the concentration at the specific target site. The expression of all these factors in a simple numerical dosage figure which would permit direct comparison between different carcinogens and species is not currently feasible. The parameters needed for expressing cancer incidence and intensity in animals include the proportion of tumour-bearing animals, multiplicity of tumours in one organ or animal, time to development of tumours, cell-type affected, and the growth rate and behaviour of the cells. Combining them into a single figure is an inaccurate over-simplification. Thus a function of dose (an independent parameter), and intensity and incidence (dependent parameters) cannot be expressed in a simple way allowing direct mathematical comparison of potency. Similar problems in expressing the exposure and response of humans limit the utility of any simple numerical index derived from epidemiological studies.

C. 1. 3. Human Data as a Basis for Potency Evaluation

Data obtained from observations on man are closest to ideal for grouping chemicals according to potency. However, these data are frequently deficient in precise information required to determine the dose, duration of exposure, and incidence.

For Proven Human Carcinogens only retrospective data-gathering is possible and in most cases the available information consists, at best, of an accumulation of case histories. For potency estimation from retrospective studies it is necessary to relate the magnitude of effects in man to the duration and levels of exposure to the particular carcinogen. However, accurate historical exposure measurements and clearly-identifiable increases in cancer in man are only rarely available. Indeed, even when an increased incidence of cancer has actually been identified, the exposure conditions occuring many years previously have to be traced back because of the long latency of chemically-induced cancer. Failure to recognise the importance of quantitative exposure data in earlier times has led, inevitably, to a general paucity of data regarding the exposure of the worker and other populations. The situation is somewhat different in occupational settings today, where worker exposure is more frequently recorded accurately. It should be noted that the data from human epidemiology is often less precise than that from animal experiments. The conditions of exposure of workers, their age, and the variety in their genetic background are quite different from the steady and well-controlled exposure conditions and genetic background in animal experiments. Moreover, the magnitude of the health effects in man is known with less accuracy than in experimental animals. Indeed, in man the cause of death is in most cases not confirmed pathologically even though the registration of mortality from cancer has been improved by the organisation of cancer registries. Because human exposure levels are usually rather low in comparison to those in animal experiments, increases in cancer incidence may be small and may remain undetected, even with easily-recognised tumour types. When the background incidence of the observed tumour is relatively high, and the type and site are common, it may be difficult to notice any small increase in this incidence.

In summary, estimating the potency of carcinogens in numerical terms is usually not possible because measurements of the level and duration of exposure have not in the past been made and recorded with the required precision and because the precise incidence in exposed and (matched) control groups is seldom available. Nevertheless, the accumulation of observations in humans often allows a rough comparison of the carcinogenic potency of the chemical to be made.

C. 1. 4. Experimental Data as a Basis for Potency Evaluation

For the majority of chemicals, especially new ones where no human data are available, the estimation of carcinogenic potency in man can be based only on extrapolation from experimental data. The first step in this estimation is the determination of the carcinogenic potency of the chemical in the experimental system. The most appropriate type of experiment from which such a determination can be made is a well designed, adequately conducted animal carcinogenicity study. Key information to be derived from such a study includes :

a) The proportion of animals bearing neoplasms at each exposure level.
   The number of neoplasms per animal.
   The number of different types of neoplasms.
   The number of species affected.

b) The magnitude of the dose at which the carcinogenic response occurs.

c) The organ or target tissue in which the carcinogenic response occurs. It should be recognised that an increase in the number of tumours of a type which occurs spontaneously in a high proportion of the strain of animal being used (e.g. liver tumours or pulmonary adenomas in certain strains of mice) carries less weight in the estimation of potency than does the appearance of tumours in other organs.

d) The latency period before tumour development. The shorter the latency period the more potent is the chemical.

e) The sensitivity of the experimental model.

f) Further information obtained from other toxicological studies such as kinetic and metabolic data. The significance of these in the estimation of potency to man is not clear in every case. Fundamental differences in genetic make-up between animals and man, which can lead to wide variations in response to the action of chemicals, include differences in immune and hormonal status, among others. Only in those situations where it can be demonstrated that the active metabolite (or ultimate carcinogen) and the mechanism of action are the same in an animal and man, and where similarities in exposure conditions, kinetics, metabolic pathways and defence mechanisms have been established, would a quantitative extrapolation of potency have more meaning.

C. 1. 5. Importance of Metabolism

In assessing the carcinogenic potency of a chemical, the fact that the concentration of the ultimate carcinogen at a specific target site is determined by the administered dose, modified by kinetics and metabolism, should be taken into consideration. Thus, the extrapolation of findings in animal studies to man has to take into account, among other factors, qualitative and quantitative differences in metabolism between test animals and man. There are many examples in which differences in metabolism between different test-animal species and even different strains can be demonstrated.

In addition, the metabolic activity within a given strain of animal may vary considerably with time and with varying experimental conditions, including dose. Such differences may result in large variations in concentration of the active metabolite at the target site.

A further problem exists in the use of data obtained in animal studies at high exposure levels for extrapolating to effects at much lower levels in animals or man. Exposure to high levels may saturate metabolic processes which at low concentrations may rapidly inactivate active metabolites resulting in a lower probability of effective reaction with the target site. Consequently, the dose-response relationship may be quite different after exposure to «high» and «low» levels. Nevertheless, a weak response at high doses generally indicates a low potency.

C. 1. 6. Importance of Mode of Action

The precise physical, chemical or biological events at the cellular level which induce malignant transformation are not known. There is, however, an association between certain events and the development of malignant neoplasms. The differentiation and division of cells is under the control of the genetic material. Interference with the integrity of DNA and its replication process may lead to the formation of abnormal cells which may develop into a neoplasm if they are outside the normal physiological control of the body. Certain chemical carcinogens have the ability to induce self-replicating errors in the genetic material and it assumed that this is a mechanism by which they induce cancer. Such chemicals are said to have genotoxic carcinogenic activity.

There is now a large body of evidence which supports the view that malignant neoplasms may be produced by chemicals which do not induce self-replicating errors in the genetic material. Such chemicals are said to have non-genotoxic activity. The exact mechanisms of action of such substances are not known, but may well be different from chemical to chemical, reflecting a combination of physical, chemical or biological alterations. Changes in hormone balance and specific enzyme systems, and effects related to immuno-suppression, may be involved in some cases. Other evidence suggests that malignant neoplasms may develop where there is repeated chemical injury to tissue.

The distinction between substances with genotoxic and those with non-genotoxic carcinogenic activity is important because it has a profound bearing on the magnitude of their dose-related carcinogenic activity. It is claimed that for genotoxic carcinogens there is no dose below which carcinogenic activity does not occur. This no-threshold concept is based on the extension to carcinogenicity of the hypothesis that there is, in general, no threshold for mutagenic events. Events due to self-replicating errors in the genetic material could result from the effect of a single molecule in a single cell, and therefore, simplistically, there is no threshold for such an event. This postulate is impossible to prove or disprove experimentally for mutagenic or carcinogenic activity. It ignores the existence of multi-stage processes in carcinogenesis, and of intracellular defense mechanisms and several other supracellular defense mechanisms. Recent evidence suggests that a threshold may exist for the mutagenic activity of chemicals in **in vitro** systems. Therefore no definitive conclusion can be made about the existence or absence of any threshold for all or some of the substances with carcinogenic activity. Even if a threshold could be established experimentally, the threshold level could not be defined in practice for genetically-heterogenous human populations.

Chemicals with non-genotoxic carcinogenic activity produce a primary toxic event prior to the carcinogenic event. For such chemicals there is no basis for presuming the absence of a threshold. For **non-carcinogenic** chemicals it is believed, and generally accepted, that a threshold for toxic effects exists. A similar no-effect dose may exist for the primary toxic activity of chemicals with a non-genotoxic carcinogenic activity, and this will be the threshold for their (secondary) carcinogenic activity.

Because of the different response of chemicals with genotoxic and non-genotoxic carcinogenic activity as a function of dose, methods proposed for potency estimation should take into account what is known about the mode of action of each chemical carcinogen.

C. 1. 7. The Use of Mathematical Models for Predicting Carcinogenic Risk at Low Doses from Long-Term Animal Studies

One unavoidable step in the process of Risk Estimation is the extrapolation from positive results obtained in animal carcinogenicity studies to man (usually exposed to substantially lower doses).

As indicated above, there is no general agreement on the question of whether a dose threshold exists below which no excess of neoplasms would be induced by a chemical with genotoxic carcinogenic activity. Furthermore, thresholds should not be confused with «no observed effect levels», which depend strongly on the resolution of the experimental system used. In the absence of sufficient information to allow the establishment of safety on the basis of the existence of a threshold as normally used in toxicology, the concept of virtual safety has been developed. In this concept, very low dose-levels are assumed to carry a certain minimal risk which is low enough to be acceptable. To obtain an idea of exposure levels associated with such minimal risk, the extrapolation of data from animal experimentation is required. In such experimentation, high dose-levels usually have to be used to produce a measurable incidence of neoplasms in the relatively small number of animals to which, for practical reasons, the experimental groups must be restricted.

In this process of extrapolation, two steps have to be clearly distinguished. The first is the extrapolation of results obtained at high dose-levels in experimental animals to predict incidence at low dose-levels which are experimentally inaccessible. The next step is the extrapolation from this calculated incidence at low dose-levels in animals to the incidence in man at the same dose-levels.

C. 1. 7. 1 Extrapolation from high to low dose-levels

In the first step of extrapolation, models based on mathematical functions of the incidences of neoplasms and dose-levels have sometimes been used. Purely statistical models are based on the assumption that dose-response curves arise from a distribution of individual thresholds within a population. Stochastic models are based on the assumption that a positive response is the result of the random occurrence of a number of biological events, and they therefore have some biological rationale. However, both types of model are based on the assumptions that the metabolic fate of the compound and the reaction of the host are strictly proportional to dose, and both reject the existence of population thresholds, although statistical models assume the existence of a threshold for individuals. Nevertheless, by using these models the expected neoplastic response of the species under investigation to the low-level exposures of interest may then be calculated from the observed incidences at higher doses.

The available mathematical models for the extrapolation from a given set of experimental data may not be appropriate for the following reasons :

i) Despite considerable effort, the mechanisms of chemical carcinogenesis are not completely understood and at present there is insufficient biological evidence to confirm the appropriateness of any particular model, or evidence that they estimate reliably the incidence at low exposure levels.

ii) By the use of suitable mathematical parameters all the models can describe a given set of data points more or less accurately and it is impossible to select the «right» model simply on goodness-of-fit criteria. This is of particular importance because in the low-dose range the cancer incidence calculated using different models and functions, derived from the same experimental results, may differ by several orders of magnitude.

iii) The fate of the chemical at the high doses normally administered in animal carcinogenicity studies may be substantially different from the fate of the chemcal at low doses because of, for example, saturation of metabolic processes and induction of enzymes involved in the metabolism of the chemical. In addition, reactive defense mechanisms and adaptive responses may not be proportional to dose. Thus the assumption made in all models that, independently of dose levels, the action and fate of the chemical are constant relative to the dose is often not fulfilled in practice.

For extrapolation to the experimentally inaccessible, low-incidence region by currently-available mathematical models an irrevocable prerequisite is the availability of data from a carefully-planned and well-conducted animal study. In addition, the application of mathematical models in Risk Estimation has to be supported by information to clarify the underlying biological processes leading to the observed effect. This may include, for instance, results from short-term tests for carcinogenicity, studies of binding to cellular macromolecules, DNA-repair studies ; metabolic and toxico-kinetic data ; and information on enzymatic alterations, the proportion of neoplasm-bearing animals, the number of neoplasms per animal, the type and site of neoplasms, and on the agressiveness of the neoplasm as expressed in its pathogenesis and time-to-occurrence.

Provided that the limitations imposed by the above assumptions and uncertainties are understood, the use of mathematical models may be appropriate as one of the techniques employed by an expert. They can, however, do nothing more than provide a first estimate of the incidence, at low exposure levels, in the animal species and strain under investigation.

C. 1. 7. 2. Extrapolation from animal data to man

The second step, extrapolation from the findings in animals to man at the dose-level of interest, is not amenable to mathematical modelling. This is because in carcinogenic studies with animals the complexity of the human situation, such as the intensity and frequency of exposure, age at first exposure, diet and genetic make-up, and species differences have to be grossly simplified. Extrapolation to man requires the expert judgement of a group with the necessary knowledge and experience to take the results from the first step in extrapolation (including mathematical modelling when appropriate), together with the factors previously discussed, in order to assess the likely qualitative and quantitative response of a human population at the estimated level of exposure. On the rare occasions when adequate epidemiological data are available, a numerical expression of the likely risk is possible. More usually, the data on which the assessment is based are inadequate for numerical expression and it will be possible to express the magnitude only in relative terms i.e. compared with other carcinogens.

At the present state of this art, mathematical models should not be used in isolation for final Risk Estimation. Needless to say, further research on the mechanisms of chemical carcinogenicity is necessary and will certainly result in the development of more versatile models. Critical application of existing models is just one step in this direction.

C.1. 8. Categorisation of Carcinogens According to Potency

In the above discussion on the evaluation of potency, some of the many pitfalls present in any attempt to make a simple extrapolation from animal experimental results to human risk have been emphasised. Nevertheless, there is a pressing need to find some acceptable way of categorising carcinogens in terms of their potency so that Risk Estimation and Limitation become possible, and appropriate control measures may be developed. By considering all available data, a categorisation according to potency can be made with reasonable confidence, although in the present state of knowledge chemical carcinogens can be categorised only into the broad classes of high, medium and low potency.

However, because the process of categorisation is neither primarily numerical nor invariable (it will differ from chemical to chemical), it is not possible at present to provide strict rules for it. This is why a group of experienced scientists is required to develop the categorisation for individual chemicals on the basis of expert judgement.

The following are some of the factors from animal and human data which would lead experts to judge that a chemical was of high carcinogenic potency :

i) a large increase in the incidence of malignant neoplasms at low exposure levels ;

ii) a large number of malignant neoplasms per individual ;

iii) a short latency period ;

iv) development of malignant neoplasms after a single dose or few doses ;

v) induction of malignant neoplasms in a variety of organs ;

vi) induction of malignant neoplasms in organs with a low natural incidence of neoplasms ;

vii) induction of a high incidence of malignant neoplasms in a number of strains and species ;

viii) ancillary information on mode of action, metabolism and tissue dose, when available.

Conversely, the following are some of the factors which may lead to categorising a chemical as one of low carcinogenic potency :

i) a small increase in the incidence of malignant neoplasms ;

ii) a long latency period ;

iii) the induction of malignant neoplasms only of a type with high and variable natural incidence ;

iv) the induction of malignant neoplasms only at grossly excessive exposure levels ;

v) the absence of carcinogenic activity in a number of species ;

vi) ancillary information on mode of action, metabolism and tissue dose, when available.

C. 2. EVALUATION OF EXPOSURE-RELATED FACTORS

C. 2. 1. General

Together with the estimation of the potency of the carcinogen, a knowledge of the conditions of exposure are of major importance for Risk Estimation. Exposure to carcinogenic substances implies their presence in the work-place under such conditions that actual or potential contact with individuals is possible. Actual contact may lead to absorption into the body, and this again may or may not lead to the development of cancer in the exposed persons. Whether cases occur depends mainly on the carcinogenic potency of the chemical, the dose and period of exposure, and factors specific to the individual which are, in the main, indeterminable. The purpose of analysing exposure-related factors is to identify the significant sources of exposure, and estimate the exposure quantitatively.

C. 2. 2. Factors Influencing Exposure

In evaluating individual exposure conditions, the following need to be considered :

a) the intrinsic properties of the substance ;

b) factors related to the process ;

c) factors related to personnel.

These are detailed in Appendix 2, and only a few of the more general aspects are discussed below.

C. 2. 2. 1. The intrinsic properties of the substance.

Certain intrinsic properties of a substance play a major role in determining whether it will be absorbed systemically. These properties include such biological parameters as bioavailability and metabolism (discussed earlier) which are interrelated with the physical properties and form of the substance. Thus, fine dusts, gases and vapours (and therefore liquids of high vapour pressure) will generally lead to greater atmospheric concentrations at the workplace and greater availability for systemic absorption by inhalation than will pastes, coarse granules, or liquids and solids of low vapour pressure. Liquids and fine dusts are more likely to cause skin contamination by splashing and/or impregnation of clothing, and if the material is also capable of penetrating intact skin the risk is enhanced. Other physical forms, though of less importance, must not be disregarded when considering dermal exposure.
Ingestion of an industrial chemical is unlikely to be an important route of entry, although it should be recognised that dust particles greater than 7 μm in size may be inhaled, trapped in the upper respiratory tract, and carried in the mucus to the pharynx where most of it will be swallowed.

C. 2. 2. 2. Factors related to the process

a) Concentration of the substance in the process. The occurrence of significant exposure depends on whether a substance is handled in the process at high concentrations, e.g. as a starting material, a major intermediate, or a final product, or at low concentrations, e.g. as a minor by-product or unstable intermediate. The actual carcinogen may occur as a contaminant or impurity in small concentration in other substances. As this concentration becomes progressively smaller the carcinogenic risk from this contaminated or impure substance will for all practical purposes disappear.

b) Handling conditions. The conditions influencing exposure during handling are more complex to assess, since such widely-varying parameters as plant design, process technology, logistics, working habits and atmospheric conditions must be taken into consideration. For example, poor handling practice can enhance workplace contamination, whereas sophisticated ventilation systems may considerably reduce it. For a thorough evaluation of the total exposure, all of these extrinsic factors must be analysed step by step for every individual technological process, including such ancillary activities as maintenance, transport, storage and disposal.

C. 2. 2. 3. Factors related to personnel

The degree or intensity of contact of individuals with a carcinogen depends on the exposure levels and duration of exposure, both of which may be influenced by the use and effectiveness of personnel protective measures.

With a given exposure level the dose of a carcinogen received will depend mainly on the duration of exposure. For a given plant design and process this duration can be reduced by a number of measures directed at the protection of the exposed individuals. These measures, such as personal protective equipment, good hygiene and training, constitute another set of factors which must be individually considered during the Risk Estimation process.

In this process, the risk to individuals should not be considered to be smaller because only a few people are exposed, and greater if a large number are exposed. In this sense, risk relates to each individual and not to a group.

C. 3. Outcome of Risk Estimation

When the Risk Estimation group has assessed the likely potency of the carcinogen to man, it considers the information available on occupational exposure. The group then uses its judgement to decide whether there is likely to be a risk of excess cancers in the exposed population in a given situation.

For the few Proven Human Carcinogens where there are good historical data on the response at given exposure levels, this judgement can be given reasonably precise limits. However, for other Proven Human Carcinogens, evidence of the likely human response must be based on an assessment of pharmacokinetics, metabolism and mode of action, as well as potency, in animal models. The judgement in this case is therefore less precise and the decision is either that under the given exposure conditions there is likely to be a risk of excess cancers in the exposed population or, alternatively, that this is unlikely.

Thus the end-result of Risk Estimation is an expert judgement of risk which is vital for the deliberations of the Risk Limitation group. It is one of the tasks of this latter group to judge what level of risk, and therefore exposure, is acceptable or reasonable.

D. RISK LIMITATION

In this final stage of risk assessment, information from the Risk Estimation stage is considered in the context of many other necessary factors, for example :

i) the social and economic advantages and penalties ;

ii) the technological feasibility and the cost of implementing the recommended control measures ;

iii) the availability of analytical and monitoring methods to measure exposure ;

iv) the existence of alternative chemicals or processes.

The end-result of this stage is the development of recommendations governing exposure conditions, the handling of the carcinogen, and any other measures necessary to ensure that the risk is controlled to a suitably low level by means which are technologically feasible and take into account the social and economic consequences of the proposals. It is of course important that the recommended level of exposure is measurable in practice, i.e. that adequate analytical and monitoring techniques are available. The recommendations may include the specification of atmospheric exposure levels for gases, vapours and dusts, and of industrial hygiene measures (including working conditions) for non-volatile liquids or solids where the main contact is other than by inhalation.

Risk Limitation should be considered by a group in which are represented the parties ultimately concerned with implementing the recommendations made to control the risk, plus experts from the Risk Estimation group. Such a group will sometimes operate within a legislative process.

As new information becomes available, a re-evaluation should be carried out in order to improve the overall risk assessment. Uncertainties in risk assessment should not lead to deliberate over- or under-estimation of risk, as either could act against the best interests of the groups most closely concerned.

When recommendations from the Risk Limitation group become available, measurements of the actual exposure or an assessment of the exposure conditions should be compared with those specified in the recommendations and, where necessary, technical or organisational changes should be made to achieve compliance with them. Generally, technological measures such as changes in the chemistry of the process or changes to the plant or ancillary equipment are most effective in reducing risk. When loss of containment of the carcinogen cannot be achieved immediately by such measures, improvements in personal protection, or other organisational measures, should be implemented but should generally be regarded as temporary. Reference back to the assessment of exposure-related factors in the Risk Estimation stage will provide important indications of the major sources of exposure, and hence of areas where effort may be most effective in reducing risk.

As far as is reasonably practicable, the number of people exposed to occupational carcinogens should be minimised by appropriate technological and organisational measures.

In the description of risk assessment given in this Monograph the need to take into account the possibility of exposure due to accidents has not so far been mentioned. However, it is very important that for Proven and Putative Human Chemical Carcinogens of **high potency,** adequate and rapid measures should be planned to detect and deal with such accidental exposure.

Only a few general remarks concerning protective measures have been made in this document because, strictly speaking, the organisation of cancer prevention at the workplace and the medical surveillance of exposed workers are not a part of risk assessment. However, risk assessment plays a decisive role in setting priorities for prevention and surveillance.

Appendix 1

CONCLUSIONS BASED ON SHORT-TERM TESTS FOR CARCINOGENICITY

Most toxicological information is quantitative, and the majority of the information in, for example, the EEC toxicological base-set is no exception. Thus, for example, the reporting of acute oral or dermal toxicity is given as an LD 50 expressed as a numerical value of dose per unit body weight. One notable exception to this rule is short-term testing for mutagenicity or carcinogenicity. There are in fact very good scientific reasons, e.g. quantitative and qualitative differences in metabolism, for not using data from short-term tests for a numerical quantification of mutagenic and/or carcinogenic **risk** in man. Such data are relevant to assessing carcinogenic **potential.**

The consequence is that the qualitative nature of the result (either positive or negative) puts particular emphasis on its accuracy. It is not possible to calculate the probability of error of a result expressed only as «positive» or «negative». This emphasises the need for a high degree of certainty that the qualitative result is correct, so that subsequent decisions are made on a sound footing.

In considering what decisions should be taken on the basis of a positive or a negative short-term test, the first and most important step is to establish that the result is «confirmed». There are several conditions which must be met before a result can be considered confirmed, and one of the most important is that the result from a second short-term test should be in agreement (see below). Carcinogenic or non-carcinogenic activity is suggested only when this and other conditions are met.

Special problems, which are not yet resolved, are presented by mixtures, and thus results from the testing of mixtures should be regarded with caution.

1. Requirements for a «confirmed» result.

For the result of testing a chemical in short-term tests to be considered «confirmed», it must meet the following criteria :

1. 1. The result should be derived from a test carried out to a protocol meeting minimum criteria (i.e. the protocol should be supported by a formal validation study) **or** the «chemical class control pairs» should have performed as expected in the same experiment. (A «chemical class control pair» is defined as a pair of chemicals, both structurally-related to the chemical under test, one of which is carcinogenic and the other non-carcinogenic).

1. 2. The result should be the same in two test systems with unrelated end-points.

1. 3. The result should be consistent with the experimental design, e.g. there should be a clear dose-response relationship ; where no increase in colonies is seen in a bacterial mutation test, it should be established that this is not due to high toxicity ; in a bacterial mutation test, an increase in colony counts should be confirmed by replicate plating.

1.4. The positive controls used to check the reliability of the test should be used in parallel with each experiment.

1.5. The result should be reproducible if performed at different times in separate laboratories.

1.6. An assessment should be made of the likely contribution of impurities to the test result. Impurities which are strongly positive in the test system or highly toxic to the test organism can lead to incorrect results.

2. An unconfirmed result

If any one of the above criteria is not met, the result becomes an unconfirmed result.

3. Consequences of a confirmed positive result

Since there are sufficient controls and checks in the experiments leading to a confirmed result, it has certain characteristics, namely : it is reproducible ; it is consistent with the known response of the tests to that chemical class ; each test is shown to have been performing accurately at the time of the experiment ; the chemical itself is responsible for the result ; and the result is the same in two tests. These controls and checks provide a result which is the best possible indication of carcinogenicity short of actually carrying out an animal carcinogenicity study, although it falls short of proof of carcinogenicity. If any one of the criteria for regarding a result as confirmed is not met, it should be considered an **unconfirmed result.**

4. Consequences of a confirmed negative result.

In the absence of other relevant toxicological data, a confirmed negative result from short-term tests is a good indication of non-carcinogenicity. However, other considerations, e.g. the size of the exposed population and the likely dose absorbed, may make it prudent to carry out additional testing in whole animal systems.

5. Consequences of an unconfirmed result

There are many occasions when the result is unconfirmed e.g. if it is positive in only one test, or if the results are not fully reproducible. An unconfirmed result is a temporary situation and generally needs further studies in order to confirm the positive result or to obtain a confirmed negative result. If the result remains unconfirmed, then expert judgement regarding the significance of the unconfirmed result is required when it is used, with all the other factors available, as one element in the process of risk assessment. Whatever decision is taken, it should be reviewed when new information becomes available and the result becomes confirmed.

The data produced by short-term tests can be considered as part of the process of identifying carcinogenic potential. Other points (including chemical and toxicological properties and exposure conditions), have to be taken into account for risk assessment and, thus, the decisions taken must be based on a consideration of all the data for each chemical and situation.

Appendix 2

DETAILS OF FACTORS INFLUENCING EXPOSURE

1. Factors Related to Intrinsic Properties of the Material

1.1. Physical and chemical properties and physical form :

- — gas
- — liquid (boiling-point, vapour pressure)
- — solid (wet or dry, particle size)
- — solubility
- — reactivity (possibility of neutralisation, etc)
- — ease of removal (in case of spill, escape)

1.2. Toxicological properties which themselves lead to a limitation of exposure, for example irritancy, corrosivity, etc.

1.3. Detectability

- — odour
- — availability of analytical methods for determining exposure level
- — availability of analytical methods for detection in effluents, exhaust air, reaction mixtures, residues, etc
- — availability of monitoring methods

2. Factors Related to the Process

2.1. Status of material under consideration in the process :

- — starting material (reactant)
- — major intermediate (isolated / not isolated)
- — minor or unstable intermediate
- — desired product
- — impurity
- — solvent or other auxiliary substance

2.2. Type of process :

- — batch
- — continuous

2.3. Size of process :

- — gross material turnover per year
- — batch size
- — number of batches per year

2.4. Processing system :

- — open / closed equipment
- — open-air or enclosed plant

2. 5. Sources of workplace contamination (exposure) in the processing system :

- — charging of materials
- — ventilation (filters, washers, cyclones, etc)
- — effluents
- — leaks (especially gases and liquids)
- — spillage (especially dusts, and splashing of liquids)
- — maintenance and repair operations
- — going on- and off-stream

2. 6. Sources of workplace contamination (exposure) in ancillary systems :

2. 6. 1. Transport

- — bulk material (especially liquids and gases)
- — packed material
- — loss of containment due to road or rail accidents
- — loss of containment due to breakage or perforation of individual containers
- — effect of small leaks (especially from punctured bags or leaking flanges)
- — means of decontamination and cleaning of vehicles and spilling areas

2. 6. 2. Storage

- — above, at or below atmospheric pressure
- — warehouse or open-air storage
- — suitability of storage area (ventilation, size, height, possibility of cross-contamination, etc)
- — fire and explosion hazards
- — handling during storage (loading, unloading, repacking, etc)

2. 6. 3. Disposal

- — residues from technological processes to be considered with respect to quantity, frequency and physical form (liquids, solids, tars, etc)
- — other materials to be disposed of e.g. packaging materials, cleaning materials, disposable protective equipment, equipment to be scrapped
- — way of disposal, e.g. burning (type, suitability and location of incinerator) ; depositing (controlled / uncontrolled, bulk / packed, above-ground / underground, geological and atmospheric conditions, etc) ; others (regeneration, recycling, shredding, etc).

3. Factors Related to Personnel

3. 1. Personal protective equipment (to be assessed for suitability, duration of use, cleaning methods, etc) :

- — protective clothing (full or partial protection)
- — goggles / face shields
- — respirators / gas masks
- — separate air supply

3. 2. Hygiene measures :

- — availability of working overalls and underwear (number ; disposable or to be washed)
- — cleaning of clothes (who, where)
- — frequency and obligation of changes
- — availability and use showers / baths
- — type and suitability of cloak-rooms
- — eating, drinking, smoking in working-area
- — ease, frequency and methods of cleaning working area
- — possibilities of spreading contaminating material outside working area (by persons)
- — protection of outsiders coming into working area (restricted areas)

3. 3. Training, instruction :

- — extent, adequacy
- — effect, identification
- — adherence

Appendix 3

TASK FORCE CARCINOGENICITY

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Appendix 4

ECETOC MONOGRAPHS, TECHNICAL REPORTS AND DOCUMENTS

TITLE	REFERENCE	DATE
«Draft for Ecological Hazard Evaluation», for 6th Amendment.	ECETOC Doc-1	19.06.79
«Comments to EPA on Proposed GLP Standards for Health Effects».	ECETOC Doc-2	20.08.79
«Comments to EPA on Proposed Health Effects Test Standards for TSCA Test Rules».	ECETOC Doc-3	03.10.79
«Good Laboratory Practice»	Monograph N° 1	Oct. 1979
«Comments to FDA on Non-Clinical Laboratory Studies», Amendment of GLP Regulations.	ECETOC Doc-4	28.12.79
ECETOC Brochure	—	May 1980
«Definition of Teratogen» for 6th Amendment.	ECETOC Doc-5	24.06.80
«Contribution to Strategy for Identification and Control of Occupational Carcinogens».	Monograph N° 2	Sept. 1980
«Definition of a Mutagen». for 6th Amendment».	See Appendix in Monograph N° 2	Sept. 1980
«Relevance of Model Experiments to Photodegradation in the Environment».	ECETOC-Doc-6	01.10.80
«Biodegradation Methodology», in 6th Amendment.	ECETOC Doc-7	28.10.80
«Abiotic Degradation Testing», in 6th Amendment.	ECETOC Doc-8	28.10.80
«Test Method for Acute Toxicity to Daphnia Magna», for 6th Amendment.	ECETOC Doc-9	28.10.80
«Skin Sensitisation», test methods etc.	ECETOC Doc-10	29.10.80
«Prolonged Toxicity Study with Daphnia Magna».	ECETOC Doc-11	24.11.80
«Criteria for Choosing Chemicals for Testing».	ECETOC Doc-12	19.12.80
«Organisation of Jointly-sponsored Studies».	ECETOC Doc-13	20.12.80
«ECETOC Statement on Formaldehyde».	ECETOC Doc-14	16.02.81
«Summary of Results Presented at the CIIT Conference on Formaldehyde Toxicity on 20-21st November 1980».	ECETOC Doc-15	27.02.81
«Assessment of Data on the Effects of Formaldehyde on Humans».	Technical Report N° 1	13.05.81
«The Mutagenic and Carcinogenic Potential of Formaldehyde».	Technical Report N° 2	18.05.81
«Assessment of Test Methods for Photodegradation of Chemicals in the Environment».	Technical Report N° 3	03.08.81
ECETOC Colloquium Photodegradation	ECETOC Doc-16	14.10.81
ECETOC Brochure, 2nd edition	—	Dec. 1981